

DETAILED ACTION

Response to Election/Restriction filed on March 10, 2008 is acknowledged. Claims 1-21 are pending in this application.

Sequence Noncompliance

Applicant is advised that the application is not in compliance with 37 CFR §§ 1.821-1.825. Applicant is required as part of a response to this action to comply with 37 CFR §§ 1.821-1.825, and that failure to do so will result in abandonment of the application. Applicant should refer to the attached "Notice to Comply" for instructions.

Restriction

1. Applicant's election of Group 17 (claims 5-8) drawn to a combination preparation comprising at least two antiviral substances, and elected species Z-DEVD-FMK for caspase inhibitor and U0126 for the kinase inhibitor in the reply filed on March 10, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
2. The restriction requirement is deemed proper and is made FINAL in this office action. Claims 1-4 and 9-21 are withdrawn from further consideration, pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable

generic or linking claims. Claim 7 is withdrawn from further consideration as being drawn to nonelected species. Ludwig et al (US 2005/0129694 A1) indicates that 1-adamantanamine, a rimantadine, a neuraminidase inhibitor or a nucleoside analog comprising ribavirin are not kinase inhibitors (see claim 8). Therefore, Claims 5-6 and 8 are examined on the merits in this office action.

Rejection-35 U.S.C. 112, 2nd

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 5 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 5 recites, "A combination preparation...wherein the combination preparation can be used in the form of a mixture or as individual components for using them simultaneously or at different times at identical or different places." The phrase "A combination preparation" is unclear. It is unclear what is meant by a combination preparation. For example, combination preparation can imply in the same tube, combination of components sequentially administered, combination preparation one administration at a time and so on. Because claim 8 depends from indefinite claim 5 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

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6. Claims 5-6 and 8 are rejected because these claims are dependent on method claims. Claims 5-6 and 8 are drawn to a product (combination preparation), and therefore, cannot be dependent on method claims.

7. Claim 8 is rejected because claim 8 do not further limit claim 5. Claim 8 is drawn to “the combination preparation according to claim 5 for the prophylaxis or therapy of an infection with negative-strand RNA viruses, comprising influenza viruses or Borna viruses.” Please note, intended use has not been given any patentable weight, since they do not further limit the compound. Therefore, claim 8 does not further limit the structure of combination preparation of claim 5.

Rejection-35 U.S.C. § 112, 1st

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 5-6 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the combination preparation of Z-DEVD-FMK and U0126 for the therapy of influenza virus *in vitro*, does not reasonably provide enablement for prophylaxis of at least one viral disease, let alone all viral diseases *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to the combination preparation comprising at least two antiviral active substance for the prophylaxis and/or therapy of a viral disease, wherein at least one active substance inhibits at least one cellular component such that a virus multiplication is inhibited.

(2) The state of the prior art:

The Merck manual indicates that there are plethora of viral diseases known. For example, the Merck manual lists a number of viruses that infect humans (see Table enclosed). Among the viruses listed are: Influenza viruses A, B, and C; Adenoviruses; Epstein-Barr virus; Rhinoviruses; Rubella virus; Human parvovirus B19; Human herpes virus type 6; Hepatitis Type A, B, C, D and E; Polioviruses; Herpes simplex virus and

Human papillomavirus (recurrent). There is also human immunodeficiency virus (HIV).

The Merck manual indicates that some infections are asymptomatic or latent. In latent infection, viral RNA or DNA remains in host cells but does not cause disease unless some trigger causes symptom recurrence (see Merck Manual, Virus, 2nd paragraph).

Furthermore, the Merck manual indicates that some viral diseases are oncogenic.

Human T-hymphotropic virus 1 (HTLV-1) predisposes to human leukemia and lymphoma; Epstein-Barr virus predisposes to malignancies such as nasopharyngeal carcinoma; Hepatitis B and C viruses predispose to hepatocellular carcinoma (see Merck manual, Virus, 5th paragraph). Additionally, the Merck manual indicates that slow viral diseases have lengthy incubations (months or years) and are often due to reactivation of a virus that caused an earlier infection (see Merck manual, Virus, 6th paragraph). According to the Merck manual, some viral diseases can be diagnosed clinically or epidemiologically. For others, definitive diagnosis is necessary mainly when specific treatment may be helpful or when the agent may be a public health threat (e.g., severe acute respiratory syndrome [SARS]) (see Merck manual, 7th paragraph).

Additionally, the Merck manual indicates that antiviral drugs are most often used therapeutically or prophylactically against herpesviruses, respiratory viruses, and HIV. Some drugs against HIV are being evaluated for other viral infections such as hepatitis B virus (HBV) (see Merck manual, Virus, Treatment and Prevention). According to the Merck manual, viral vaccines include influenza, measles, mumps, poliomyelitis, rabies, rubella, hepatitis A, B, varicella, and yellow fever (see Merck manual, Virus, Vaccines and immune globulins).

Furthermore, not all antiviral agents have been found to treat HIV-1. The Merck manual indicates that HIV is caused by the retrovirus HIV-1, and infection leads to progressive immunologic deterioration and opportunistic infections and malignancies (see Merck manual, HIV, p.1, 1st paragraph). Further, the Merck manual indicates that diagnosis is made using serum antibody tests (see Merck manual, HIV, Diagnosis); Opportunistic infections, particularly *Pneumocystis pneumonia*, progressive neurologic disease, and severe wasting, are associated with poor prognosis (see Merck manual, HIV, Prognosis). The Merck manual indicates that there are nearly 2 dozen ARV drugs, including multidrug combination products, available in the US, each of which may have adverse effects and drug interactions with other ARV drugs or commonly used antibiotics, anticonvulsants, and sedatives. Combination of drugs include nucleoside analog reverse transcriptase inhibitors given in combination with either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (see Merck manual, HIV, Treatment). Additionally, the Merck manual indicates that vaccines against HIV have been difficult to develop because of the extreme mutability of HIV surface proteins that results in an enormous diversity of antigenic types (see Merck manual, HIV, Prevention). Most of the prevention of the transmission of HIV listed in the Merck manual is public education, safe sex practices, HIV testing, etc (see Merck manual, HIV, Prevention). The combination drug therapy for HIV-1 infection mostly consists of anti-retroviral drugs such as nucleoside analog reverse transcriptase inhibitors, protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

Furthermore, Takizawa et al (*Microbiol. Immunol.*, 1999, 43(3): 245-252, filed with IDS) teach the involvement of caspases in influenza virus-induced apoptosis using caspase inhibitors. The reference teaches that z-VAD-FMK and z-IETD-FMK effectively inhibited virus-induced apoptosis, whereas Ac-DEVD-CHO and Ac-YVAD-CHO showed partial and little effect on virus-induced cell death. The reference teaches that the peptide inhibitors of caspases used in this study did not inhibit viral replication. The authors concluded that influenza virus infection activates some caspases, and that this activation may be downstream of viral replication (see abstract). Additionally, Wurzer et al (*European Molecular Biology Organization*, 2003, 22(11): 2717-2728, filed with IDS) indicate that virus-induced caspase activity could be efficiently suppressed by Z-DEVD-FMK (see p. 2719, left column, bottom 1st sentence). The reference indicates that caspase activity is required for efficient influenza virus propagation. However, viral protein synthesis appears not to be affected by the caspase inhibitor. The reference cites Takizawa et al work described above, and states that "virus-induced cell death could be inhibited by peptide caspase inhibitors, there was no effect on viral protein synthesis...this strongly suggests that all the early events in the viral life cycle, such as virus entry, genome release, transcription and replication, as well as translation of early and late viral proteins, are not affected by caspase action" (see 2719, right column, lines 7-9 and 20-24).

The art provide guidance to how to treat some viral diseases such as influenza, herpes virus, hepatitis, etc, but does not provide how to determine individuals who are susceptible to all viral diseases. HIV-1 infections are treated with multidrug cocktail of

reverse transcriptase inhibitor and protease inhibitor or non-nucleoside reverse transcriptase inhibitors. The Merck manual indicates that vaccines against HIV have been difficult to develop and public education, safe sex practices, etc have lowered the transmission rate. However, none of the prior arts provide guidance as how to determine individuals who are susceptible to all viral diseases, how to determine which combination of antiviral agents would make proper combination, and how to treat or prevent such viral diseases such as HIV when only certain inhibitors have been found to work in such cases (i.e., not all antiviral agents would work to treat or prevent HIV-1).

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Applicant's activity is based on the determination of predicting those who are susceptible to viral diseases. Additionally, Applicant's activity is based on the determination that the combination of antiviral active agents. Since the activity is based on determining the patient population that is susceptible to viral diseases, and determining the combination of the active agents, the predictability in the art is low. This is due to the fact that the art has recognized the difficulty in determining the patient population who are susceptible to viral diseases. Furthermore, due to the fact that there are vast numbers of antiviral active agents having so many different structures, it would be hard to predict how to combine these anti-viral agents and how to determine which

one to pick from the vast numbers of the antiviral agents and kinase inhibitors to make proper combination.

The claim doesn't identify the patient population, therefore, the claim implies that anyone can be protected against viral diseases, even the cells on Petri dishes. However, the Applicant has not shown who will be susceptible to any viral diseases. Applicant's specification shows prophetic examples, where only the *in vitro* data are shown to one combination of the antiviral agent/kinase inhibitor.

Additionally, as indicated above, Takizawa et al (*Microbiol. Immunol.*, 1999, 43(3): 245-252) teach the involvement of caspases in influenza virus-induced apoptosis using caspase inhibitors. The reference teaches that z-VAD-FMK and z-IETD-FMK effectively Inhibited virus-induced apoptosis, whereas Ac-DEVD-CHO and Ac-YVAD-CHO showed partial and little effect on virus-induced cell death. The reference teaches that the peptide inhibitors of caspases used in this study did not inhibit viral replication. The authors concluded that influenza virus infection activates some caspases, and that this activation may be downstream of viral replication (see abstract). Furthermore, Wurzer et al (*European Molecular Biology Organization*, 2003, 22(11): 2717-2728) data also support the Takizawa reference that the caspase inhibitor does not inhibit the viral replication. Since Takizawa et al and Wurzer et al both teach that the caspase inhibitors do not inhibit viral replication, there is no evidence that the combination of two caspase inhibitors would work to inhibit the viral replication. If one caspase inhibitor (acting as an antiviral agent) did not inhibit viral replication, then adding another caspase inhibitor (acting as an antiviral agent) would not act to inhibit viral replication. The viral disease is

not known, and not all compounds would work on all viruses. There are too many variables between the experimentation, how to determine the patient population, how to combine the antiviral agents (i.e. to pick antiviral agents to make a proper combination), thus, it clearly shows the unpredictability of the art.

(5) The breadth of the claims:

The claims are drawn to a combination preparation for the prophylaxis or therapy of at least one viral disease, comprising at least two antiviral substances, wherein at least one antiviral active substance is a caspase-3, caspase-9, caspase-8 and other caspase inhibitors. Further, claims are drawn to combination preparation of at least one cellular caspase inhibitor and at least one antivirally acting substance that is a kinase inhibitor.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

The specification provides guidance on how the virus multiply in wildtype and in caspase-3 deficient cells; mechanism of inhibition of virus multiplication by a caspase inhibitor; additive effect of a caspase inhibitor and a kinase inhibitor in inhibition of the virus multiplication (see Examples 1-3). It is unclear as to when to administer the compound and the patient population. Example 1 provides the analysis of caspase 3, and the important role the caspase-3 plays in the influenza virus multiplication. The effect of inhibitor on the expression of early or late viral proteins were investigated in

A549 cells and MDCK and vero cells. The caspase-3 inhibitor Z-DEVD-FMK showed dose dependent reduction of the influenza virus titers, and the example concludes by stating that caspases, in particular caspase-3 are target points for an anti-influenza virus prophylaxis or therapy. Example 3 provides an additive effect of Z-DEVD-FMK and U0126 (kinase inhibitor) on the inhibition of the virus multiplication. The specification discloses that A549 cells and caspase-3-deficient MCF-7 cells were infected with influenza A virus strain fowl plague virus (FPV) in presence of DMSO, the caspase-3 inhibitor Z-DEVD-FMK or the MEK inhibitor U0126 (see paragraph [0067]). The specification discloses that the inhibition of caspase-3 infected cells led to a reduced cleavage of the caspase substrate PARP, not to a reduced activity of the Raf/MEK/ERK signal pathway. The inhibition of MEK by U0126 efficiently inhibited the virus-induced activity of ERK, did not lead to a modified cleavage of PARP. The specification concludes that the caspase-3 dependent cascade and the Raf/MEK/ERK signal pathway mediate independently from each other through different processes (see paragraph [0069]). As stated above, the specification implies that combination of Z-DEVD-FMK and U0126 would lead to a synergistic inhibitory effect on the virus replication (see paragraph [0070]). The working examples are limited to A549 cells, MDCK cells, and vero cells, and the caspase-3 inhibitor or U0126 (kinase inhibitor) is administered separately or independently of each other (see paragraph [0067]). Again, the specification only shows the individual administration of Z-DEVD-FMK and U0126, and the specification has not shown any examples of other antiviral agents that are caspase inhibitors and other kinase inhibitors that are antiviral agents. There are too

many variables between the experimentation, thus, it clearly shows the unpredictability of the art. The specification does not disclose other time points or time frame, other animal models and other opioids that are effective against stress-induced blood pressure crash.

The specification has not provided guidance in the way of a disclosure to how to determine individuals that need protection against viral diseases, and determine which antiviral agents would make proper combination, since there are so many different antiviral agents and kinase inhibitors known in the art. Furthermore, as indicated above, some of the agents may react negatively with one another in such cases as HIV therapy: adverse effects and drug interactions with other ARV drugs or commonly used antibiotics, anticonvulsants, and sedatives. There is no clear guidance as to how to determine the patient population. Since the prior art is still unclear as to who are susceptible to viral diseases, more guidance is necessary.

(8) The quantity of experimentation necessary:

Since it is uncertain to predict the patient population who are susceptible to viral diseases, the Applicant have not provided the appropriate time frame at which the combination preparation should be administered, and which antiviral agent would make with different antiviral agent, including kinase inhibitors, one of ordinary skill in the art would be burdened with undue “painsstaking experimentation study” to determine if the antiviral agent combination would be effective in protecting anybody from viral diseases.

Please note that the term "prevent" or "prophylaxis" is an absolute definition which means to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic" or "treat" or "alleviate", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes)- including preventing such all viral diseases, such as HIV-1, which is clearly not recognized in the medical art as being totally preventable condition.

10. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient."

MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must

describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a combination preparation for the prophylaxis or therapy of at least one viral disease comprising at least one active substance and at least one antivirally acting substance, which is a kinase inhibitor. The generic statements combination preparation of at least one active substance that inhibits cellular caspase and at least one antivirally acting substance which is a kinase inhibitor does not provide ample written description for the combination preparation and compounds that are kinase inhibitors that are antiviral agents, since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 6 is broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of compounds that are kinase inhibitors and function as antiviral agents. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is “not sufficient characteristic for written description purposes, even when

accompanied by a method of obtaining the claimed sequence.” MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of peptide or peptidomimetic molecules that functions as a kinase inhibitor that qualify for the functional characteristics claimed as a antivirally acting substance.

The specification is limited to the U0126 (MEK inhibitor) as the antivirally acting substance that is a kinase inhibitor (see Examples 2-3). The specification discloses that the inhibition of the Ras-Raf-MEK-ERK signal transduction pathway by active substances, which selectively inhibit one or several of kinases involved in this signal transduction pathway, for instance the MEK and/or the SEK, the intracellular multiplication of intranuclearly replicating negative-strand RNA viruses, for instance of influenza A virus and the Borna disease virus (BDV). The working example describes only the MEK inhibitor U0126 (see Examples 2-3). The specification discloses 1-adamantanamine, a rimantadine, a neuraminidase inhibitor or a nucleoside analog comprising ribavirin, which are not kinase inhibitors (see Ludwig et al., US 2005/0129694 A1). The specification does not describe any other kinase inhibitors that are antivirally acting, such as peptide or peptide-like molecule that act as kinase inhibitors. Description of U0126 for MEK inhibitor (antivirally acting kinase inhibitor) is

not sufficient to encompass numerous other kinase inhibitors that belong to the same genus. The specification only teaches one combination preparation (i.e., Z-DEVD-FMK and U0126). Since only one caspase inhibitor combination with one kinase inhibitor (U0126) is described, and no other combination is described, how does one skilled in the art know which kinase inhibitor to pick that would make a proper combination? For example, there are varying lengths, varying amino acid compositions, small organic molecules having varying composition and numerous distinct qualities that make up the genus of kinase inhibitors. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed. The Applicant was not in possession of all possible combination of cellular caspase inhibitors and kinase inhibitors that have antiviral activity.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982.

The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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